UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,776	10/05/2000	Richard D. Granstein	2650/1F966-US1	8709

7590 11/13/2002

Darby & Darby PC
805 Third Avenue
New York, NY 10022

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/679,776	Applicant(s) GRANSTEIN, RICHARD D.	
	Examiner Q. Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 21, 2002 has been entered.

The amendment and the Declaration under Rule 132 submitted on April 23, 2002 has been entered and assigned as Papers # 10 and #11. Claims 7 and 24 have been amended, claims 1-31 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 stand rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for suppressing tumor growth in experimental mice by *intradermal* administration of total tumor cell RNA or epidermal cells pulsed *ex vivo* with total tumor RNA, wherein said RNA is from tumor cells of the same type in the host,

does not reasonably provide enablement for protecting *any* subject from *any* and *all* tumors, or treating any tumor in human by any route of administration, and it does not reasonably provide enablement for protecting a subject from *any* and *all* pathogens such as microbial pathogens, or for inducing tolerance to any and all antigens by any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The applicant asserts in Paper #11 that the specification, when considered with the teachings of the state of the art at the time of the invention, enables the full scope of the claimed invention both in the area of induction of protective immunity and induction of tolerance for the antigens encompassed by the scope of the claims. Applicants submitted another Declaration under Rule 132 (paper #11), and 17 references to show the state of the art and the levels of the skill, and to support the arguments.

The Exhibits, Declaration, and arguments have been carefully considered along with the previous Declaration under Rule 132 (paper #6). However, they are not sufficient to overcome the standing rejection for the following reasons.

With respect to the 17 references, they could not be used to support the enablement aspect of the RNA vaccine because none of the references are directed to RNA vaccine or immunization; none of the references are directed to inducing tolerance to an autoantigen, an allergen, or a transplant antigen; and none of the references are directed to a successful RNA vaccination in humans. It is not appropriate to use the references of DNA vaccination as the sole support for RNA vaccination for immune

tolerance induction and for immunization against any and all pathogens, because, as cited in the first Office action and taught by *Mitchell et al*, the mode of action for DNA and RNA vaccines are simply distinct, they both have their advantages and drawbacks, a thorough comparison of the function of DNA and RNA vaccines has not been done or known in the art (see Section bridging pages 177-178 of *Mitchell et al*). It is particularly true concerning the issue of RNA delivery because the disadvantage of the RNA vaccine is the stability, that RNA could be easily degraded by numerous factors. For example, *Qui et al* teach that although using mRNA to transfer genetic information is highly desirable, success in utilizing *in vivo* RNA delivery for transgene expression has been extremely limited, partially due to RNA instability and to the lack of an efficient intracellular delivery mechanism applicable to a wide variety of tissue or organ systems. Even though the applicant has shown that one type of tumor antigen survived the intravenous injection, it does not provide sufficient support commensurate with the scope of the claim to indicate that any pathogen cellular total RNA would survive the intravenous delivery and mount a sufficient immune response.

With respect to the route of immunization, applicants argue, "*the method and route of administration may affect the degree of immunity engendered, not that an immune response could not reasonably be predicted by one of skill in the art*". This is found not persuasive because assuming any route of administration would engender an immune response, strong or weak, claims call for induce an immune response to a pathogen" or "protecting a subject from a cancer", thus would be evaluated by that standard. A weak response to a pathogen from other route of administration may not

generate a protective response, thus, the degree of immunity matters by this standard. A satisfying disclosure should provide at least a few representative routes of delivery showing the protective effects, interestingly, the specification and declaration only provide evidence to the contrary, which will be discussed in details in the immediate following paragraphs.

In paper #10, the applicant argues that the Declaration (paper #11) demonstrates that the claimed invention, i.e., tolerization is achieved and therefore fully enabled, that the literature available at the time of the invention documents that administration of protein antigens by the intravenous route induces immunologic tolerance.

The applicant is reminded that instant claims drawn to tolerance induction are not limited to intravenous administration; that it is not appropriate to use the result of protein vaccine as the support for RNA vaccination; that it is not appropriate to use tolerization to tumor antigen as the support for any type of antigens (which will discussed in detail later in this Office action). With regard to tolerance induction of a tumor antigen by intravenous injection, the specification or the Declaration fails to provide an enabling disclosure for the full scope of the claims. The specification teaches that anti-tumor immune stimulation, not tolerance, was achieved by intradermal administration of total tumor RNA or ECs pulsed *ex vivo* with tumor RNA (Examples 1-3), whereas intravenous injection of tumor RNA induced tolerance to subsequent tumor antigen challenge (example 4). Such tolerance was detailed in Paper #11, wherein the tumor RNA was injected intravenously to a recipient, the recipient T lymphocytes were then adoptively transferred to naïve mice, which naïve mice were then received footpad

injection of EC pulsed with tumor RNA, and subsequent test shown that the DTH response to tumor antigen of these mice (received adoptive transfer and intradermal EC) was reduced. Apparently, different immunization regime produced different effects, the intradermal injection provided protective effect whereas addition of adoptive transferring T lymphocytes activated by intravenous injection in another subject provided tolerance effect to the same tumor antigen in the same type of animal. Therefore, the applicant's own disclosure supports the unpredictability of immune response via different routes of total RNA administration, and is contradictory to the claims and the instant argument. It is noted that claims 16-23 are drawn to inducing immune *tolerance* to an antigen using any route of administration; whereas claims 1-7 are drawn to inducing immune *response* to an antigen using any route of administration, it is unclear how the same method step would cause two opposite effects, the specification lacks support for such contradictory claims, thus fails to provide an enabling disclosure for the full scope of the claims.

With respect to the types of pathogens and antigens encompassed by the claims, the different antigens have their own distinct characteristics and mechanisms of operation. It is not appropriate to use the references of DNA vaccine for tumor or influenza virus as evidence for RNA vaccination for microbial, allergen, autoantigen or transplantation antigen. This is because as stated in Papers #5 & #8, the mode of action of an immune response is distinct for different type of pathogen, allergen or autoantigen. *Yu and Restifo* (J Clin Invest 2002 Aug;110:289-94) teach that many of the strategies learned in the development of highly successful vaccines against infectious agents

simply do not apply to cancer vaccines (1st paragraph, page 289). For example, would the tolerance to HIV be induced if the HIV RNA were to give to AIDS patients? As for tolerance to autoantigen, it is well known in the art that tolerance to self-antigens is an essential feature of the immune system, and an autoimmune disease is caused by the loss of such essential feature in the host, wherein the mechanism of such loss is still largely unknown and most likely involves defects of the host immune system. Therefore, simply administering an autoantigen as an attempt to reestablish the feature of self-tolerance is unlikely to be successful and has not been shown otherwise in the instant specification. As for vaccines for bacterial infections, *Strugnell et al* (Immunl Cell Biol 1997;75:364-69) review "DNA VACCINES AGAINST BACTERIAL INFECTIONS ARE UNDER REPRESENTED IN THE DNA VACCINE LITERATURE. THIS COULD REFLECT EITHER POOR RESULTS USING THIS TECHNOLOGY IN THE CONTEXT OF BACTERIAL INFECTIONS.(...), THE USE OF DNA VACCINES IN BACTERIAL INFECTIONS MAY BE COMPLICATED BY FUNDAMENTAL DIFFERENCES BETWEEN PROKARYOTIC AND EUKARYOTIC GENES AND GENE PRODUCTS, INCLUDING MRNA STABILITY, CODON BIAS, SECONDARY STRUCTURES SURROUNDING NATIVE START SEQUENCES AND GLYCOSYLATION." (abstract) "THE MAGNITUDE OF THE RESPONSE OBSERVED FOLLOWING VACCINATION WITH BACTERIAL ANTIGEN GENES ARE CONSISTENTLY MUCH LESS THAN THOSE ELICITED BY VIRAL DNA VACCINES. THE CHALLENGE TO SCIENTISTS INTERESTED IN PURSUING THIS EXCITING TECHNOLOGY IN THE CONTEXT OF BACTERIAL VACCINES WILL BE TO ADDRESS THIS RELATIVELY POOR IMMUNOGENICITY." (page 368, "potential problem section). Even though *Yu et al* and *Strugnell et al* discuss the DNA vaccine, they illustrated the differences among different type of antigens, the unpredictability of the immunogenicity for each type of antigens and thus the distinctiveness of the host response. In view of the state of the art and the

level of those skilled in the art, it is concluded that without actual reduction to practice, i.e. experimental evaluation, the results of making and using claimed invention will be highly unpredictable in such a variable art, and one skill in the art could not use the results from tumor RNA to predict the effect of other types of antigen RNAs without undue experimentation as it is broadly claimed.

With respect to the types of *tumor antigens* encompassed by the claims, claim 1 embraces cross reactivity of any and all tumors, but all the working examples and the Declarations shown that a tumor suppressive effect is achieved with RNA from the same type of tumor cells. Whether this protective effect could extend to other types of tumors are highly unpredictable. For example, *Ashley et al* (J Exp Med 1997;186:1177-82) teach that DCs pulsed with SMA560 RNA did not protect against CNS challenge with B16 cells (last paragraph, page 1179). Cancer immunotherapy is complicated by the fact that in order for tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen(s). Before the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional b_2m expression, and loss of particular MHC class I alleles (*Restifo et al* (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would prevent the tumor from being recognized by the tumor specific cytotoxic T cells, these mechanisms are expected to differ in different types of tumors, and administration of

total tumor RNA would not circumvent the problem. Almost a decade later, the list of proposed mechanisms for tumor escape has not become shorter (*Yu & Restifo*, J Clin Invest 2002 Aug;110:289-94, paragraph bridging the left and right column in page 292), even though many progresses have made it possible to induce an anti-tumor response in many occasions, "MOST OF THESE RESPONSES TURNED OUT TO BE PARTIAL AND TRANSIENT, AND MOST RESPONDING PATIENTS EVENTUALLY SUCCUMBED TO PROGRESSIVELY GROWING TUMOR" (left column, page 292).

In the Declaration under Rule 132, the applicant indicates that the claimed invention is effective in reducing the rate of tumor growth in two mouse tumor models. However, as indicated in Paper #5 & #8, the skilled artisan, *Mitchell et al, McCluskie et al,* and *Boucher et al* have concluded that what shows effective in mouse is not predictable in humans. "WHEN THESE VIRUSES WERE TRIED IN THE CLINIC, IT BECAME APPARENT THAT EXPERIMENTS IN ANIMAL MODELS HAD FAILED TO PREDICT KEY ASPECTS OF RECOMBINANT VACCINE FUNCTION IN PEOPLE" (*Yu & Restifo*, J Clin Invest 2002 Aug;110:289-94, paragraph bridging the right column in page 291). "WE DO NOT YET HAVE A CANCER VACCINE IN HAND THAT CAN RELIABLY INCREASE PATIENT SURVIVAL OR INDUCE TUMOR DESTRUCTION",

For the reasons of record advanced in papers #5 and #8 and those set forth foregoing, the instant specification fails to meet the statutory enablement requirement for the broad scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-7, 11, 12, and 16-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because claims 16-23 are drawn to inducing immune tolerance to an antigen using any route of administration, including intravenous, oral, or intranasal administration; whereas claims 1-7, 11, 12, and 31 are drawn to inducing immune response to an antigen using any route of administration. These two groups of claims use virtually the same method steps but engendered opposite effects, it is unclear how such dual effects could be achieved.

Claim 16 is vague and indefinite because the subject of the antigen RNA administration has not been identified in the claim.

Claims 24-27 are vague and indefinite because claim 24 recites a tumor antigen, whereas the dependent claims 25-27 recite an autoantigen, an allergen, and a transplant antigen. It is the common knowledge in the art that a tumor antigen does not embrace an autoantigen, an allergen, and a transplant antigen, thus, there is insufficient antecedent basis for the recitation of claims 25-27.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24 and 30 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Quip et al* (Gene There 1996;3:262-68) for the reason of record and set forth following.

Applicants argue that *Qui et al* does not disclose the claimed invention because the compositions of *Qui et al* do not meet the standards required for *in vivo* deliver into humans required by the present invention.

In response, this issue has been addressed in the final rejection that the art-known carrier composition used for gene gun delivery does not appear different in animal models and in humans. In the working example, the pharmaceutical carrier for the RNA is normal saline, which could be used in both humans and animals. Further, beside firefly Lucifer's, *Qui et al also* delivered *human* growth hormones and *human* alpha-1 antitypic to mice, which clearly indicate that the mouse study is set forth as feasibility study for humans, therefore, the formulation for mice should be applicable in humans. Thus, *Qui et al* still anticipate the instant claims.

Claims 24 and 30 are newly rejected under 35 U.S.C. 102(b) as being anticipated by *Corny et al* (Cancer Rees 1995;55:1397-1400).

Corny et al teach a composition comprises mRNA transcripts encoding human carcinoembryonic antigen (CEA) and delivering such to mice in vivo (3rd paragraph, page 1398). Thus, *Conry et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7, 8, 9, 13, 14, 24, and 28-31 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Ashley et al* (J Exp Med 1997 Oct;186:1177-82), in view of *Beissert et al* (J Immunol 1995;154:1280-86).

Claims 1-3, 5, 7, and 31 are directed to a method comprising administering to epidermal cells total pathogen cell RNA, wherein the total cell RNA is administered *in vitro* to epidermal cells, wherein the pathogen is tumor, wherein an immune response to the pathogen could be elicited. Claims 8, 9, 13, 14, 24, and 28-30 are directed to a composition comprising total RNA or mRNA encoding an antigen of the pathogen cell. The specification defines the epidermal cells as cells enriched for Langerhans cell content (page 2, line 18).

Ashley et al teach a method for treating brain tumors comprising pulsing an antigen presenting cell *in vitro* with RNA obtained from total B16 tumor RNA, which induced specific CTL against B16 tumor cells (abstract). *Ashley et al* go on to teach "THE ADVANTAGES OF VACCINATING WITH TOTAL TUMOR-DERIVED MATERIAL ARE THAT THE IDENTITY OF THE TUMOR ANTIGEN(S) NEED NOT BE KNOWN AND THAT THE PRESENCE OF MULTIPLE TUMOR ANTIGENS REDUCES THE RISK OF ANTIGEN-NEGATIVE ESCAPE MUTANTS." (right column, page 1177). *Ashley et al* use bone marrow-derived dendritic cells, do not particularly teach using epidermal cells as APC.

Beissert et al teach that Langerhens cells are dendritic antigen presenting cells that resides in the epidermals and have been shown to induce lymphocyte-mediated immune response in a variety of experimental systems both in vitro and in vivo, and that they are particularly indicated in tumor immunity (1st paragraph, page 1280).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Ashley et al,* by simply selecting the epidermal cells as the APC of choice as taught by *Beissert et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the critical role of ECs in anti-tumor immunity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The following new grounds of rejection are applied because these claims encompass an *in vitro* process of producing an RNA-loaded antigen presenting cell that present on its surface a tumor antigenic epitope encoded by the RNA, wherein the epitope induces T cell proliferation (i.e. claim 1 of US 5,853,719).

The applicant submitted a Declaration under Rule 131 previously (paper #6) to antedate the cited patent. Upon reconsideration, the Declaration could not antedate the cited patent because the claimed subject matter in the instant application is obvious variants of the claims of cited patent(s). Under such circumstance, the Declaration could not overcome the rejection because MPEP sets forth, "PRIOR INVENTION MAY NOT BE ESTABLISHED UNDER THIS SECTION IF EITHER: (1) THE REJECTION IS BASED UPON A U.S. PATENT OR

U.S. PATENT APPLICATION PUBLICATION OF A PENDING OR PATENTED APPLICATION TO ANOTHER OR OTHERS WHICH CLAIMS THE SAME PATENTABLE INVENTION AS DEFINED IN § 1.601(N); OR (2) THE REJECTION IS BASED UPON A STATUTORY BAR". (M.P.E.P. § 1.131); and "WHEN THE CLAIMS OF THE REFERENCE AND THE APPLICATION ARE DIRECTED TO THE SAME INVENTION OR ARE OBVIOUS VARIANTS, AN AFFIDAVIT OR DECLARATION UNDER 37 CFR 1.131 IS NOT AN ACCEPTABLE METHOD OF OVERCOMING THE REJECTION". ((See details in M.P.E.P. 706.02(b) and M.P.E.P. 2300.02)).

Claims 1-3, 5, 7, 8, 9, 13, 14, 24, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Nair et al* (US 5,853,719, IDS), in view of *Beissert et al* (J Immunol 1995;154:1280-86).

Nair et al teach a method comprising pulsing an antigen presenting cell *in vitro* with RNA obtained from a tumor cell or pathogen cell RNA (claims 1, 2, 6, 7, 8, 10, 14, and 16). *Nair et al* go on to TEACH "EVEN UNFRACTIONATED RNA PREPARATION (E.G., TOTAL RNA OR POLY A+ RNA) CAN BE USED." and "IF DESIRED, THE PREPARATION CAN BE FURTHER FRACTIONATED WITH RESPECT TO THE RNA (E.G., BY SUBTRACTIVE HYBRIDIZATION) SUCH THAT "TUMOR-SPECIFIC" OR "PATHOGEN-SPECIFIC RNA IS PRODUCED." (Column 3, lines 29-35) Nair et al go on to teach that the tumor RNA pulsed APC could elicit a CTL response in vitro or in vivo (column 9, lines 13 through column 12). The composition taught by *Nair et al* comprises the total pathogen cell RNA, total mRNA or RNA encoding an antigen. *Nair et al* teach that the antigen-presenting cell is preferably a dendritic cell or a macrophage. *Nair et al* do not particularly teach using epidermal cells as APC.

Beissert et al teach that Langerhens cells are dendritic antigen presenting cells that resides in the epidermals and have been shown to induce lymphocyte-mediated

immune response in a variety of experimental systems both in vitro and in vivo, and that they are particularly indicated in tumor immunity (1st paragraph, page 1280).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Nair et al,* by simply selecting the epidermal cells as the APC of choice as taught by *Beissert et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the critical role of ECs in anti-tumor immunity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 5, 7, 8, 9, 13, 14, 24, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Nair et al* (US 6,306,388), in view of *Beissert et al* (J Immunol 1995;154:1280-86).

The cited patent is the continuation of the '719 patent, and further claim the total tumor RNA (claim 13), and other pathogen RNA (including virus and bacterial cell RNA, (claims 18-21).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Nair et al,* by simply selecting the epidermal cells as the APC of choice as taught by *Beissert et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the critical role of ECs in anti-tumor

immunity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
October 30, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER